PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 38/51 — A1

(11) International Publication Number: **WO 96/01648**

(43) International Publication Date: 25 January 1996 (25.01.96)

(21) International Application Number: PCT/US95/08608

(22) International Filing Date: 7 July 1995 (07.07.95)

(30) Priority Data:
273,109 8 July 1994 (08.07.94) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/273,109 (CIP)
Filed on 8 July 1994 (08.07.94)

(71) Applicant *(for all designated States except US)*: IBEX TECHNOLOGIES R AND D, INC. [CA/CA]; 5485 Pare, Montreal, Quebec H4P 1P7 (CA).

(71)(72) Applicant and Inventor: ZIMMERMANN, Joseph [US/US]; 13450 Nicolet Avenue, Elm Grove, WI 53122 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: VLODAVSKY, Israel [IL/IL]; 6 Shevo Street, Gilo, 93845 Jerusalem (IL). BENNETT, D., Clark [US/CA]; 4965 Hortie, Pierrefonds, Quebec H4Y 1Z4 (CA). DANAGHER, Pamela [CA/CA]; 5219 Dalou, Montreal, Quebec H3V 2G4 (CA). BROUGHTON, Richard [CA/CA]; 3590 Ridgeway Avenue, No. 207, Montreal, Quebec H3V 1C2 (CA).

(74) Agent: PABST, Patrea, L.; Arnall Golden & Gregory, 2800 One Atlantic Center, 1201 West Peachtree Street, Atlanta, GA 30309-3450 (US).

(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ATTENUATION OF WOUND HEALING PROCESSES

(57) Abstract

Glycosaminoglycans, including heparinases 1, 2 and 3 as well as chondroitinases AC and B from the Gram negative bacteria *Flavobacterium heparinum*, can be used either separately or in combination to manipulate cell proliferation. In one embodiment, heparinases are administered to degrade heparan sulfate components of the extracellular matrix, thereby allowing the heparin binding growth factors which are stored in the extracellular matrix to migrate to adjacent cells. The mobility of chemoattractant agents, growth factors and cells also can be increased by treating tissues with glycosaminoglycan degrading enzymes, both chondroitinases and heparinases. The enzymatic removal of chondroitin sulfates from cell surfaces effectively increases the availability of growth factor receptors on the cell's surface. Selectively removing heparan sulfate from cell surfaces while leaving the extracellular matrix intact, conversely, inhibits cell proliferation by down regulating the cell's response to growth factors. This is achieved by targeting heparin or heparan sulfate degrading activites to the cell surface. Targeting the heparin degrading activity can be achieved by genetically engineering a ligand binding functionality into the heparinase proteins, or by physically controlling the localized enzyme concentration through the method of administration.